Obesity and Risks for Malignant Melanoma and Non-Melanoma Skin Cancer: Results from a Large Danish Prospective Cohort Study

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TO THE EDITOR

Obesity has increased alarmingly during recent decades in the Western world and is a risk factor for several cancers (World Cancer Research Fund, 2007; Lahmann *et al.,* 2010). However, evidence has not been fully established for an association between obesity and malignant melanoma (MM) and non-melanoma skin cancer (NMSC). Recently, results from a large meta-analysis showed that men with high body mass index (BMI) had an increased risk for MM, whereas no association between BMI and risk for MM was found among women (Sergentanis *et al.,* 2013). Fewer studies have addressed the associations between BMI and risk for NMSC and the results are conflicting (Gerstenblith *et al.,* 2012; Nagel *et al.,* 2012; Pothiawala *et al.,* 2012). However, the vast majority of studies used only BMI as a measure of obesity, although it is increasingly accepted that hip circumference (HC), waist circumference (WC), and waist:hip ratio (WHR) more accurately reflect a person's body fat distribution (Pischon *et al.,* 2008).

We here addressed the association between obesity, measured as BMI, WC, HC, and WHR, and risks for MM and NMSC, by the use of data from the prospective Danish Diet, Cancer, and Health Cohort study including 57,053 participants enrolled from 1993 to 1997. A detailed description of the cohort has been provided elsewhere (Tjonneland *et al.,* 2007). At the time of study enrollment, i.e., at baseline, information on anthropometric measures was obtained by trained healthcare professionals who measured height, weight, WC, and HC by standardized procedures (Rinaldi *et al.,* 2012). Information on potential confounders, including skin reaction to the sun and numbers of freckles and moles on the arms, was obtained from questionnaires, whereas information on vital status and migration was obtained from linkage to the Central Population Register. MM cases diagnosed in the cohort during the study period were identified by linkage to the Danish Cancer Registry, whereas all NMSC cases were identified through linkage to an already established NMSC database (Birch-Johansen *et al.,* 2010), which contains all incident cases of basal cell carcinoma (BCC) and squamous cell carcinoma (SCC) diagnosed in Denmark registered in either the Danish Cancer Registry or in the Danish Registry of Pathology. Incident skin cancers from the Danish Cancer Registry were classified according to the International Classification of Diseases, 10th edition (ICD-10), codes C43 (MM) and C44 (NMSC) and to the International Classification of Diseases Oncology 3rd edition (ICD-O-3), as MM (morphology codes M-872–879), BCC (M-809), or SCC (M-807). Data on NMSC cases from the Danish Registry of Pathology were classified by Danish SNOMED classification topography codes T01 and T02 and relevant morphology codes as either BCC (M-809) or SCC (M-807). From both registries, only invasive cancers were included (morphology codes with '3' as the last digit). Each cohort member was followed from date of cohort entry until diagnosis of MM, BCC and/or SCC, date of death/emigration, or end of follow-up on 31 December 2010.

In a Cox proportional hazard model, we examined associations between the various anthropometric measures and gender-specific rates of MM, BCC, and SCC. We used age as the underlying time axis to ensure that all analyses were based on comparisons of cohort members at the same age. Time under study was included as the time-dependent variable and modeled by a linear spline. Two-sided 95% confidence intervals (CIs) for estimated hazard ratios (HRs) were calculated with the Wald test of the Cox regression parameter.

In all, 26,685 men and 29,243 women were eligible for analysis (Supplementary Figure S1 online). A total of 357 cohort members developed MM, 3,465 developed BCC, and 341 developed SCC within a median follow-up period of 14.4 years. Table 1 shows the distribution according to quartile of BMI of the study participants. In general, men had higher WC and WHR compared with women, whereas women had a higher HC compared with men.

No convincing associations were found between the anthropometric measures and risk for MM (Supplementary Table S1 online). Women with a BMI in the highest quartile had a decreased risk for BCC of 0.67 (95% CI: 0.54–0.82) in comparison with women with a BMI in the lowest quartile, whereas no association was found between higher BMI and risk for BCC in men. Among women, every 2 $kg\,m^{-2}$ increase in BMI was associated with a decreased risk for BCC of 0.90 (95% CI: 0.86–0.94). Inverse linear dose–response associations were observed between increasing WC and WHR and risk for BCC in both

Abbreviations: BCC, basal cell carcinoma; BMI, body mass index; CI, confidence interval; HC, hip circumference; HR, hazard ratio; MM, malignant melanoma; NMSC, non-melanoma skin cancer; SCC, squamous cell carcinoma; UVR, UV radiation; WC, waist circumference; WHR, waist:hip ratio

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Table 1. Characteristics of 55,928 participants enrolled in the Danish Diet, Cancer, and Health study (1993–2007) according to BMI

Characteristic	Quartile of BMI ($kg\,m^{-2}$)			
	1	2	3	4
No. of participants (%)	11,962 (21.4%)	12,950 (23.2%)	14,225 (25.4%)	16,792 (30.0%)
Men	6,204 (23.3%)	6,605 (24.8%)	5,993 (22.5%)	7,883 (29.5%)
Women	5,758 (19.7%)	6,345 (21.7%)	8,231 (28.2%)	8,909 (30.5%)
No. of participants with MM (%)	76 (21.3%)	81 (22.7%)	93 (26.1%)	107 (30.0%)
Men	37 (19.7%)	42 (22.3%)	44 (23.4%)	65 (34.6%)
Women	39 (23.1%)	39 (23.1%)	49 (29.0%)	42 (24.9%)
No. of participants with BCC (%)	861 (24.9%)	896 (25.9%)	898 (25.9%)	810 (23.4%)
Men	429 (25.7%)	475 (28.4%)	384 (23.0%)	383 (22.9%)
Women	432 (24.1%)	421 (23.5%)	514 (28.7%)	427 (23.8%)
No. of participants with SCC (%)	85 (24.9%)	90 (26.4%)	78 (22.9%)	88 (25.8%)
Men	53 (26.1%)	54 (26.6%)	40 (19.7%)	56 (27.6%)
Women	32 (23.2%)	36 (26.1%)	38 (27.5%)	32 (23.2%)
Mean age at entry (years ± SD)				
Men	55.9 ± 4.3	56.1 ± 4.4	56.1 ± 4.4	56.2 ± 4.4
Women	56.0 ± 4.4	56.0 ± 4.3	56.4 ± 4.4	56.7 ± 4.4
Mean BMI (kg/m^2 ± SD)				
Men	22.4 ± 1.3	25.0 ± 0.6	27.0 ± 0.6	30.9 ± 2.8
Women	20.5 ± 1.2	23.0 ± 0.6	25.4 ± 0.9	30.8 ± 3.6
Mean waist circumference (cm ± SD)				
Men	85.9 ± 5.6	92.2 ± 4.9	96.9 ± 5.0	106.4 ± 8.4
Women	71 ± 5.2	76.1 ± 5.3	81.7 ± 6.0	93.8 ± 9.9
Mean hip circumference (cm ± SD)				
Men	94.3 ± 4.4	98.3 ± 4.0	101 ± 4.1	106.5 ± 6.3
Women	93 ± 4.6	97.6 ± 4.3	102 ± 4.7	110.5 ± 8.3
Mean waist:hip ratio (ratio ± SD)				
Men	0.9 ± 0.1	0.9 ± 0.1	1.0 ± 0.1	1.0 ± 0.1
Women	0.8 ± 0.1	0.8 ± 0.1	0.8 ± 0.1	0.9 ± 0.1

Abbreviations: BCC, basal cell carcinoma; BMI, body mass index; MM, malignant melanoma; No., number; SCC, squamous cell carcinoma; SD, standard deviation.

genders and between increasing HC and risk for BCC among women but not among men (Table 2). No associations were observed between the anthropometric measures and risk for SCC among men. Among women, WC, HC, and WHR did not affect the risk for SCC, but every $2\,kg\,m^{-2}$ increase in BMI was associated with a decreased risk of 0.80 (95% CI: 0.68–0.94) (Supplementary Table S2 online).

Our null findings for MM correspond with results from a meta-analysis by Olsen *et al.* (2008). Results from two other meta-analyses (Renehan *et al.*, 2012; Sergentanis *et al.*, 2013), observed an increased risk for MM among men with higher BMI but no association among women. In line with our results, most previous studies also observed an inverse association between BMI and risk for BCC. In one of the largest cohort studies to date, Pothiawala *et al.* (2012) observed that obese participants with a BMI $>30\,kg\,m^{-2}$ had a 19% lower risk for BCC compared with participants with a BMI $<25\,kg\,m^{-2}$. The only previous study of the association between measures of obesity other than BMI and risk for BCC found no convincing associations between WC and WHR and risk for BCC (Olsen *et al.*, 2006). Two cohort studies have investigated the association between BMI and SCC: In agreement with our study, Pothiawala *et al.* (2012) found that increasing BMI was associated with a decreasing risk for SCC among women but not among men, whereas Nagel *et al.* (2012) found no association with BMI in either gender.

Hence, despite the fact that several biological mechanisms link obesity to cancer risk (Calle and Kaaks, 2004), our results, which are in accordance with the majority of other studies, indicate an inverse association between obesity and risk for NMSC even after adjustment for potentially confounding factors related to UV radiation (UVR) susceptibility. However, the main limitation of our

Table 2. HRs for BCC among 26,685 men and 29,243 women according to anthropometric measures

Anthropometric measure	Men		Women	
	Cases/male cohort	Adjusted HR (95% CI)[1]	Cases/female cohort	Adjusted HR (95% CI)[1]
	1,671/26,685		1,794/29,243	
BMI[2]				
1st quartile	429/5,775	1.00	432/5,326	1.00
2nd quartile	475/6,130	1.07 (0.93–1.23)	421/5,924	0.88 (0.76–1.01)
3rd quartile	384/5,609	1.00 (0.85–1.18)	514/7,717	0.83 (0.72–0.97)
4th quartile	383/7,500	0.85 (0.69–1.05)	427/8,482	0.67 (0.54–0.82)
Per 2 $kg\,m^{-2}$		0.96 (0.90–1.01)		0.90 (0.86–0.94)
Waist circumference[3]				
1st quartile	465/6,348	1.00	497/6,234	1.00
2nd quartile	488/6,414	1.05 (0.92–1.21)	445/6,574	0.90 (0.79–1.03)
3rd quartile	382/5,722	0.97 (0.83–1.13)	397/6,377	0.86 (0.74–0.99)
4th quartile	336/6,530	0.83 (0.68–1.01)	455/8,264	0.85 (0.72–1.01)
Per 5 cm		0.94 (0.90–0.98)		0.96 (0.93–0.99)
Hip circumference[4]				
1st quartile	496/6,843	1.00	487/6,370	1.00
2nd quartile	454/6,493	0.99 (0.87–1.14)	482/6,934	0.95 (0.83–1.08)
3rd quartile	401/5,688	1.08 (0.92–1.25)	402/6,270	0.92 (0.80–1.06)
4th quartile	320/5,990	0.94 (0.77–1.14)	423/7,875	0.86 (0.72–1.02)
Per 5 cm		0.98 (0.92–1.04)		0.96 (0.92–1.00)
Waist:hip ratio[5]				
1st quartile	468/6,307	1.00	494/6,809	1.00
2nd quartile	467/6,595	0.96 (0.85–1.09)	476/6,341	1.04 (0.91–1.18)
3rd quartile	415/6,064	0.94 (0.82–1.07)	447/8,053	0.78 (0.69–0.89)
4th quartile	321/6,048	0.78 (0.68–0.91)	377/6,246	0.88 (0.77–1.01)
Per 0.05 unit		0.93 (0.89–0.97)		0.94 (0.91–0.98)

Abbreviations: BCC, basal cell carcinoma; BMI, body mass index; CI, confidence interval; HR, hazard ratio.

[1]Adjusted for age, sun sensitivity (redness, pain, and blistering; redness, pain, and peeling; redness, then tan, or only tan), degree of freckling (none, few, moderate, or many), and number of nevi (none, few, moderate, or many). Further, BMI is adjusted for waist circumference, and waist circumference and hip circumference are mutually adjusted.

[2]BMI quartiles, men: 1:$\leqslant$24 $kg\,m^{-2}$, 2:>24–$\leqslant$ 26 $kg\,m^{-2}$, 3:>26–$\leqslant$ 28 $kg\,m^{-2}$, 4:>28 $kg\,m^{-2}$; women: 1:$\leqslant$22 $kg\,m^{-2}$, 2:>22–$\leqslant$ 24 $kg\,m^{-2}$, 3:>24–$\leqslant$ 27 $kg\,m^{-2}$, 4:>27 $kg\,m^{-2}$.

[3]Waist circumference quartiles, men: 1:$\leqslant$89 cm, 2:>89–$\leqslant$95 cm, 3:>95–$\leqslant$101 cm, 4:>101 cm; women: 1:$\leqslant$73 cm, 2:>73–$\leqslant$ 79 cm, 3:>79–$\leqslant$ 86 cm, 4:>86 cm.

[4]Hip circumference quartiles, men: 1:$\leqslant$96 cm, 2:>96–$\leqslant$ 100 cm, 3:>100–$\leqslant$104 cm, >104 cm; women: 1:$\leqslant$95 cm, 2:>95–$\leqslant$100 cm, 3: >100–$\leqslant$105 cm, 4: >105 cm.

[5]Waist:hip ratio quartiles, men: 1:$\leqslant$0.91, 2:>0.91–$\leqslant$ 0.95, 3:>0.95–$\leqslant$ 0.99, 4:>0.99; women: 1:$\leqslant$0.75, 2:>0.75–$\leqslant$ 0.79, 3:>0.79–$\leqslant$0.85, 4:>0.85.

study was that we were unable to adjust for the direct UVR exposure acquired by each individual as we had no information of sun seeking behavior or use of tanning beds. As it has been suggested that obese people have a different UVR seeking behavior compared with lean people (e.g., spend less time outdoors and avoid sunbathing) (Gerstenblith *et al.*, 2012), the inverse associations observed between obesity and risk for NMSC may therefore at least partly be influenced by unmeasured confounding by UVR exposure.

Several strengths of this study are noteworthy. First, the vast majority of earlier studies only included BMI, whereas we also addressed the association between other anthropometric measures and risk for skin cancer. However, as we found no conspicuous patterns of associations between the different anthropometric measures and risk for skin cancer, we were unable to draw firm conclusions about whether general, abdominal, or gluteofemoral obesity is the best measure for analyzing potential associations with skin cancer. Another strength was that the anthropometric measures were obtained prospectively by healthcare professionals using standardized methods, thus minimizing the possibility of differential recall bias. The study population

was randomly selected from the background population, and there was virtually no loss to follow-up because of the precise linkage between the study cohort and various Danish health registries.

In conclusion, the results of this large population-based cohort study showed no convincing association between obesity and risk for MM, whereas inverse associations were found between various anthropometric measures and risk for BCC in both genders and for SCC among women only. Additional studies with more accurate data on exposure to UVR are needed to investigate the role of obesity in skin cancer pathogenesis.

CONFLICT OF INTEREST

The authors state no conflict of interest.

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SUPPLEMENTARY MATERIAL

Supplementary material is linked to the online version of the paper at http://www.nature.com/jid

REFERENCES

Birch-Johansen F, Jensen A, Mortensen L *et al.* (2010) Trends in the incidence of nonmelanoma skin cancer in Denmark 1978-2007: Rapid incidence increase among young Danish women. *Int J Cancer* 127:2190–8

Calle EE, Kaaks R (2004) Overweight, obesity and cancer: epidemiological evidence and proposed mechanisms. *Nat Rev Cancer* 4:579–91

Gerstenblith MR, Rajaraman P, Khaykin E *et al.* (2012) Basal cell carcinoma and anthropometric factors in the U.S. radiologic technologists cohort study. *Int J Cancer* 131:149–55

Lahmann PH, Cust AE, Friedenreich CM *et al.* (2010) Anthropometric measures and epithelial ovarian cancer risk in the European Prospective Investigation into Cancer and Nutrition. *Int J Cancer* 126:2404–15

Nagel G, Bjorge T, Stocks T *et al.* (2012) Metabolic risk factors and skin cancer in the Metabolic Syndrome and Cancer Project (Me-Can). *Br J Dermatol* 167:59–67

Olsen CM, Green AC, Zens MS *et al.* (2008) Anthropometric factors and risk of melanoma in women: a pooled analysis. *Int J Cancer* 122:1100–8

Olsen CM, Hughes MC, Pandeya N *et al.* (2006) Anthropometric measures in relation to basal cell carcinoma: a longitudinal study. *BMC Cancer* 6:82

Pischon T, Nöthlings U, Boeing H (2008) Obesity and cancer. *Proc Nutr Soc* 67:128–45

Pothiawala S, Qureshi AA, Li Y *et al.* (2012) Obesity and the incidence of skin cancer in US Caucasians. *Cancer Causes Control* 23:717–26

Renehan AG, Tyson M, Egger M *et al.* (2008) Body mass index and incidence of cancer: a systematic review and meta-analysis of prospective observational studies. *Lancet* 371: 569–78

Rinaldi S, Lise M, Clavel-Chapelon F *et al.* (2012) Body size and risk of differentiated thyroid carcinomas: findings from the EPIC study. *Int J Cancer* 131:1004–14

Sergentanis TN, Antoniadis AG, Gogas HJ *et al.* (2013) Obesity and risk of malignant melanoma: a meta-analysis of cohort and case-control studies. *Eur J Cancer* 49:642–57

Tjonneland A, Olsen A, Boll K *et al.* (2007) Study design, exposure variables, and socioeconomic determinants of participation in Diet, Cancer and Health: a population-based prospective cohort study of 57,053 men and women in Denmark. *Scand J Public Health* 35:432–41

(2007) *World Cancer Research Fund/American Institute for Cancer Reseach: Food, Nutrition, Physical Activity, and the Prevention of Cancer: A Global Perspective*. AICR: Washington DC. http://www.dietandcancerreport.org/cancer_resource_center/downloads/Second_Expert_Report_full.pdf. Accessed 12 January 2014

Incidence and Mortality of Neurofibromatosis: A Total Population Study in Finland

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TO THE EDITOR

We report a total population study on the incidence and mortality of neurofibromatosis 1 (NF1) and 2 (NF2). The results show that the birth incidence of NF1 is higher than that generally reported. These results also show that this life-threatening disease is more deleterious to women than to men. NF1 is an autosomal dominant neurocutaneous disease caused by mutations in the *NF1* gene on chromosome 17 (for review see Jouhilahti *et al.*, 2011). NF2 is also a dominantly inherited disease, but caused by mutations in the *NF2* gene on chromosome 22 (Rouleau *et al.*, 1993). An important milestone for NF studies was the consensus conference of National Institutes of Health (NIH) in 1987, which outlined the clinical diagnostic criteria for NF1 and NF2 (Stumpf *et al.*, 1988). Four main diagnostic signs of NF1 are visible in skin: café-au-lait spots, dermal neurofibromas, axillary freckles, and some plexiform neurofibromas. The hallmarks of NF2 include bilateral vestibular schwannomas, other schwannomas, and intracranial meningeomas (Evans *et al.*, 1992).

Most of the NF1 epidemiological studies report prevalences between 1/3,000 and 1/6,000 and birth incidence with estimates varying between 1/2,558

Abbreviations: ICD, International Classification of Diseases; NF, neurofibromatosis; SMR, standardized mortality ratio

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